

AUG 17 2003

SEQ. ID. No. 4, SEQ. ID. No. 5, SEQ. ID. No. 6, SEQ. ID. No. 7, SEQ. ID. No. 8, SEQ. ID. No. 9, and SEQ. ID. No. 10, [SEQ. ID. No. 11, SEQ. ID. No. 12, and, SEQ. ID. No. 13]

wherein the probe is contacted with the sample under conditions in which the probe specifically hybridizes under stringent conditions [selectively] with the target polynucleotide sequence to form a stable hybridization complex; and

detecting the formation of a hybridization complex, wherein an amplification of said target polynucleotide sequence indicates that said cell is a neoplastic cell.

28. (Once amended) The method of claim 26, wherein the nucleic acid sample is a metaphase spread or [a] an interphase nucleus.

REMARKS

Status.

Claims 26-28, and 37-38 are pending with entry of this amendment, claims 1-25, 29-36, 39-40, and 41-47 being cancelled and no claims being added herein. Claims 26 and 28 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification (*see, e.g.*, page 2, lines 22-25, page 3, lines 16-18, Example 1, *etc.*).

Claims 26-28, 37-38, and 41 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 26-28, and 41 were rejected under 35 U.S.C. §112, first paragraph. Claims 26-28, 37-38, and 41 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over WO9401548 in view of Accession Number Q63862 (28 Jan 1995). Claims 26-28, 37-38, and 41 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over WO9401548 in view of either of Accession Numbers W05407 or N70546. Applicants respectfully traverse these rejections.

Renumbering of claims.

Applicants note that the specification as filed contained two claims both numbered as claim 1 followed by claims 2-46. Applicants further note that these claims have been renumbered as claims 1-47.

Restriction requirement.

Applicants note the restriction requirement made final. Accordingly Applicants have canceled non-elected claims 1-25, 29-36, 39-40, and 42-47 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. §

35 U.S.C. §112, Second Paragraph.

Claims 26-28, 37-38, and 41 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the following reasons:

- 1) Claim 26 is allegedly indefinite for reciting non-elected SEQ ID Nos.
- 2) Claim 26 is allegedly indefinite for recitation of "hybridizes selectively"; and
- 3) Claim 41 is allegedly indefinite in the recitation of "is used".

Applicants respectfully traverse by argument and amendment.

Claim 1 is amended herein to recite only SEQ ID No: 9 and SEQ ID No: 10, and thereby recites only elected SEQ ID Nos. Claim 26 is amended to recite "specifically hybridize under stringent conditions" instead of "hybridizing selectively". Claim 41 is cancelled herein. Applicants believe these amendments obviate the rejections under 35 U.S.C. §112 and the rejections should therefore be withdrawn.

Applicants note that these amendments are made solely to address rejections under 35 U.S.C. §112, second paragraph, and not to address rejections in light of the prior art. Applicants expressly state for the record that the amendments made herein do not preclude the use of the Doctrine of Equivalents as applied by an appropriate court. Applicants are clearly entitled, absent amendments in view of the prior art, to assert claims issue from this application against infringers under the Doctrine of Equivalents (*see, e.g. Warner-Jenkinson Co. v Hilton Davis Chem.* 41 USPQ2d 1865 (1997), *Litton Systems Inc. v Honeywell Inc.* 46 USPQ2d 1341 (Fed. Cir. 1998)).

35 U.S.C. §112, First Paragraph.

Claims 26-28 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide enablement commensurate with the scope of the claims. According to the Examiner, claims 26 only recites that the probe hybridizes

selectively to the target, which will not distinguish a neoplastic cell from a normal cell because the normal cell is expected to carry the target sequence as well. Claim 41 was rejected because it would allegedly require additional steps to utilize the recited probe sequence to identify a mutation in the target sequence simply by the formation of a hybridization complex. Applicants respectfully traverse.

Claim 26 is amended herein to recite:

detecting the formation of a hybridization complex, **wherein an amplification of said target polynucleotide sequence indicates that said cell is a neoplastic cell.** [emphasis added]

One of skill in the art would appreciate that it is not expected that healthy (non-neoplastic) cells would show an amplification of the recited target sequence(s). The claim, as amended clearly provides a method of distinguishing neoplastic from non-neoplastic cells.

Moreover, specification expressly illustrates the detection of amplifications of the recited sequences (*see, e.g.*, Example 1) and detailed methods are described for the identification of amplifications (*see, e.g.*, pages 32-42). The specification thus teaches one of ordinary skill in the art how to detect neoplastic cells without undue experimentation. The rejection of claims 26-28 under 35 U.S.C. §112, first paragraph, should therefore be withdrawn. In view of the cancellation of claim 41, the rejection of claim 42 under 35 U.S.C. §112, first paragraph, is moot.

35 U.S.C. §103(a).

Claims 26-28, 37-38, and 41 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over WO9401548 in view of Accession Number Q63862 (28 Jan 1995). Claims 26-28, 37-38, and 41 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over WO9401548 in view of either of Accession Numbers W05407 or N70546. In particular the Examiner asserted that WO9401548 teaches a method of detecting comprising contacting a nucleic acid sample with a probe derived from a fragment of polynucleotide sequence and forming a detectable hybridization complex. The Examiner acknowledged that the sequences recited in the pending claims were not taught by WO 9401548 and relied on the cited Accession numbers for sequences allegedly corresponding to those recited in the pending claims. Applicants respectfully traverse these rejections.

The Examiner is reminded that a *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger*, 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In the instant case, Applicants explain below that the combination of the cited art fails to teach or suggest the association between the amplification of the target sequence and neoplasias. Accordingly the cited art fails to teach or suggest the claimed invention or to provide a reasonable expectation of success.

A) The cited art fails to teach an association between the amplified target sequences and a neoplasias.

The cited Accession numbers (Q63862, WO5407, and N70546) are simply listings of expressed sequence tags (ESTs). These listings provide no information whatsoever to indicate that the sequence is amplified in a neoplastic cell. Thus, for example, Accession Number N70546 simply identifies the sequences as a nucleic acid sequence found in (presumably healthy) fetal lung tissue. WO5407 is simply identified as a *Homo sapiens* clone similar to a mouse P10076 zinc finger protein. The listing provides no indication of neoplasias or amplification of the sequence. While Q63862 is identified as a sequence identified by PCR for tumor specific DNA, this listing also provides no indication that the Q63862 nucleic acid is amplified in a tumor.

The accession number listings offer thus offer no teaching or suggestion that the listed sequences are amplified in neoplastic cells. This defect is not remedied by WO 94/01548. The WO 94/01548 PCT publication simply identified 1,193 different nucleic acid fragments and teaches methods of assaying for the presence of such sequences. None of these sequences are related to the sequences identified in the present application. The combination of the cited art thus offers no teaching or suggestion that the target sequences identified in the presently pending application are amplified in neoplastic cells.

Absent any teaching whatsoever, that the target sequences recited in the pending claims are amplified in neoplastic cells, the cited art **cannot** teach or suggest the presently claimed methods. Similarly, absent any teaching or suggestion that the recited

target sequences are amplified in neoplastic cells, the cited art cannot provide a reasonable expectation of success that such sequences can be used for the detection/identification of neoplastic (e.g. cancer) cells.

The Examiner has thus failed to make her *prima facie* case, and the rejection of claims 26-28, 37-38, and 41 under 35 U.S.C. §103(a) should be withdrawn.

35 U.S.C. §101.

Claims 36-37 were provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 35-36 of copending Application No: 08/731,499.

Applicants note that this is a provisional double patenting rejection. Should the claims be allowed in this application, identical claims will be canceled from the 08/731,499 application.

Obviousness-type double patenting.

Claims 26-28, 36-37, and 41 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 24-26, 35-36, and 38 of copending Application No: 08/731,499. Claims 26-28, 36-37, and 41 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 26-28, 37-38, 56-57, and 61-63 of copending Application No: 08/785,532. Applicants note that this is a provisional double patenting rejection. Should the conflicting claims be patented, Applicants will provide a Terminal Disclaimer upon an indication of otherwise allowable subject matter.

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 217-6021.

Respectfully submitted,



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Encl: 1) Petition for 3 month extension of time.